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THE SIGNIFICANCE OF CERTAIN INTERNAL CONDITIONS OF THE ORGANISM IN ORGANIC EVOLUTION

FIRST PAPER. THE REGULATION OF THE PHYSICO-CHEMICAL CONDITIONS OF THE ORGANISM[1]

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THE desirability of an attack on the general problems of evolution from the point of view of physiology, as well as the general deficiency of literature in physiology bear-

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ing on these problems, has been recognized for some time.[2] The considerations to be presented in the papers of this series are in part the outgrowth of experimental work on the central nervous system and its relation to the processes of evolution;[3] they were in part suggested by Blackman's[4] paper on the manifestations of the principles of chemical mechanics in living matter; and they have gradually grown up in our minds as our attention was attracted more and more to the questions involved. The bearing upon the processes of evolution of certain of the facts drawn from the experimental study of the comparative physiology of the nervous system will, for the most part, be presented in separate papers embodying the experimental data. The relation of the physico-chemical conditions of the organism, together with those nervous mechanisms with which the maintenance of the physico-chemical conditions is inextricably bound up, to the questions of adaptation and fitness of the organism will constitute the greater part of the subject matter of this and following papers on the general problems of evolution from the point of view of the physiologist.

Since the inception of the work, there have appeared, in addition to Blackman's paper, several other papers of interest to physiologists on certain phases of the problem of evolution.

Woods[5] has collected the better-known cases of modification in animals and plants induced by changes in the environment or in the general conditions of existence, as shown by changes in the rate of growth, changes of the external form of the body, the occurrence of artificial

[2] Howell, "Problems of Physiology of the Present Time," Congress of Arts and Sciences, Universal Exposition, St. Louis, 1904, Vol. V, p. 11 of the reprint.

[3] Pike, *American Journal of Physiology*, 1909, XXIV, p. 124; *Ibid.*, 1912, XXX, p. 436; *Quarterly Journal of Experimental Physiology*, 1913, VII, p. 1; *Popular Science Monthly*, 1914, p. 403; *Science*, N. S., XI, p. 805.

[4] Blackman, *Nature*, 1908, LXXVIII, p. 556; AMERICAN NATURALIST, 1908, XLII, pp. 633–664.

[5] Woods, *Popular Science Monthly*, 1910, p. 313.

parthenogenesis, the modification of mental and moral traits, and the extent of regeneration of lost parts. When arranged in the order of their position in the taxonomic scale, organisms show a steadily decreasing response, with reference to these phenomena, to changes in the environment. Woods does not indicate, except in very general terms, the physiological mechanisms involved in bringing about this diminishing effect of the environment. Some years earlier Donaldson[6] had called attention to the general lack of influence of formal educational training upon the course of later life of talented individuals.

Julian Huxley[7] in his discussion of the individual in the animal kingdom, points out that the individual acquires an increasing independence of the environment, or that the environment has a diminishing effect. Huxley assigns mere increase in size and the increasing complexity and efficiency of the nervous system as two of the factors involved in the attainment of the freedom from mere accidents.

Mathews[8] has pointed out more specifically some of the various internal mechanisms which are involved in the acquisition of independence of the environment on the part of the higher animals. These are, according to him, (1) the heat-regulating mechanism, (2) the mechanism of immunity, (3) the mechanism for rendering animals independent of external conditions of moisture, (4) the mechanism which renders them independent of barometric pressure, (5) the mechanisms for reproduction and caring for the young, (6) the alimentary mechanism, and (7) the nervous system.

Henderson[9] has shown that the environment is an external thing in which certain physico-chemical conditions are kept relatively constant, while others may vary

[6] Donaldson, "Growth of the Brain," London and New York, 1895, pp. 347, 355, 360, 365.

[7] Huxley, J. S., "The Individual in the Animal Kingdom," Cambridge and New York, 1912.

[8] Mathews, AMERICAN NATURALIST, 1913, XLVII, pp. 90–104.

[9] Henderson, "Fitness of the Environment," New York, 1913.

widely, even in the same region. As long as organisms live in the ocean or in the water generally, they are subjected to certain relatively constant conditions dependent upon the physico-chemical properties of the environment. But it should be recognized that with organisms which have migrated out upon the land the case is somewhat different, as all conditions, except oxygen concentration and pressure, vary more markedly on the land than in the water. Temperature, in particular, varies greatly over the land, and the poikilothermal animals have their activities greatly limited by the temperature conditions.

From Henderson's premises, the conclusion follows that life is what it is because the environment is what it is. A different environment might, and in all probability would, have resulted in, or been associated with, a different form of life on the earth. Certain characteristics commonly called adaptations are, as Henderson shows, the automatic and inevitable results of the physico-chemical conditions obtaining in the environment. If such a view assumes that an adaptation ceases to be an adaptation when the manner of its origin is discovered, it would seem that we were in need of a more precise definition of adaptation. The question arises whether other similar characteristics that have been called adaptations are not also the inevitable and automatic result of the physico-chemical conditions of the environment. We may therefore consider the question of the reality of adaptation, and also whether some of the characteristics of organisms are not really adaptations,[10] even if they arise from the action of physico-chemical conditions in the environment. Again, since, in a given environment, with essentially the same physico-chemical conditions for all its inhabitants, there are many animal types, it would appear that there were some influences operative within the organism itself to produce certain characteristic reactions, known as adaptations, to the environment. As we will show subsequently, these facts do not in any way preclude an explanation of their origin on some hypothesis

[10] Mathews, *loc. cit.*

other than vitalism. The organisms may be, under certain conditions at least, more variable than the environment. These considerations apply also to those simple organisms which are the cellular constituents of a larger body. Certain of the higher vertebrates, in which, as has been indicated, the influence of the environment is probably less than in some of the lower forms, are more variable than certain of the lower vertebrates.

It is a fair inference from the facts cited in the various papers referred to, that certain characteristics of living matter, such as its slight degree of alkalinity, and its relatively great specific heat, may be regarded as the direct automatic and inevitable results of the properties of the environment. Other characteristics, as the peculiar type of the nervous system, are not so obviously the direct and inevitable result of the environment, and these may be regarded, for some time to come, as adaptations to the environment or to the general conditions of existence in which the particular organism is able to live and perpetuate itself.

A statement of the general problem may now be made. Two general classes of organisms live in a relatively constant environment, so far as the general internal conditions of the organism are concerned. (1) For example, the lower marine organisms of fairly limited distribution live in an external environment which changes but little in temperature, osmotic pressure, inorganic salt content, neutrality or faint alkalinity, oxygen and carbon dioxide concentration, and soluble nitrogen compounds. Temperature and amounts of light may vary somewhat throughout the year, but the temperature changes in the given region of the ocean are less in magnitude than the temperature changes over a corresponding area of land. The osmotic and inorganic salt relationships of organism and environment alike vary but little. Nor does the organism, in general, maintain within itself, any purely physico-chemical condition differing greatly from that in the general external environment. This does not pre-

clude the origin within the marine organism of stereochemical isomers, the great importance of which has recently been pointed out by Reichert.[11] Stability of conditions would even favor the perpetuation of such compounds as could be formed under a given set of conditions. (2) On the land, as has already been indicated, the higher animals—birds and mammals—have acquired a relative independence of the environment as shown by their wide distribution. Their internal conditions of temperature, moisture and the like, may not only differ greatly from the same conditions in the environment at any given time, but the internal conditions, as we shall show, do not change greatly when the external conditions change. Intermediate between these two types is a third type which lives in an environment subject to wide variations of temperature and moisture, and whose internal temperature varies with the change of external temperature. While some of the internal conditions of these organisms remain relatively stable, others are subject to wide variation. We have then to explain, in terms of function, (1) what are the various mechanisms by which the higher animals have attained this relative independence of the environment and (2) what has been the rôle of these mechanisms in organic evolution.

II. The General Constancy of Internal Conditions in the Higher Organisms

The study of the internal physico-chemical relationships of higher animals has led to the acquisition of a considerable mass of facts concerning this phase of animal organization. These facts show that in the higher animals there exist a number of mechanisms which interact to bring about a remarkable constancy of internal physico-chemical conditions during the life of the animal. It appears justifiable again to call attention to some of these facts with a brief description of some of the mechanisms involved in order better to emphasize some of the interpretations of, and inferences drawn from, them in so far

[11] Reichert, *Science*, 1914, N. S., XI, pp. 649–661.

as these interpretations and inferences have to do with the general problem of evolution. We may, then, first of all briefly review the more salient of these facts, and afterward attempt their interpretation in terms of well-known physico-chemical laws—*e. g.*, the law of mass action and the phase rule.

1. *Thermo-Regulation in the Higher Organisms*

We may divide the vertebrates into two general groups on the basis of their internal or body temperature; (1) those which maintain a relatively constant internal temperature and (2) those whose internal temperature is variable. These groups may be tabulated as follows:[12]

TABLE I

I. Animals with a constant body temperature.

Adults or partly grown mammals and birds	about 42° C. or 107° F. Birds. about 39° C. or 102° F. Mammals. about 37° C. or 98.6° F. Man.

II. Animals with an inconstant body temperature.

(*a*) Animals which die when the temperature falls below 20° C.	Newborn mammals and birds.
(*b*) Animals which become torpid when the temperature falls below 20° C.	Hibernating forms—some mammals.
(*c*) Animals which remain active when the temperature falls below 20° C.	Reptiles, batrachians, fishes, among vertebrates; molluscs, insects, and the invertebrates generally.

Looking now to the differences between lower and higher vertebrates, to restrict ourselves at the start to a relatively small part of the animal kingdom, one of the most noticeable changes has been the development of a very constant body temperature in the so-called warm-blooded or homoiothermal animals (Table II). The detailed enumeration of the body temperature of all the animals so far observed would require too much space, but the following data will be sufficient to show upon what basis of fact the statements rest:

[12] Richet, Dictionnaire de Physiologie, 1898, t. III, pp. 85–86.

TABLE II

TABLES OF BODY TEMPERATURE

1. *Birds*

Genus or Species	No. of Observations	Temperature	Observer
Sparrow	1	42.1° C.	Davy.
Turkey	1	42.7	Davy.
Peacock	1	40.5 to 43.0	Davy.
Guinea fowl	1	43.0	Davy.
Duck, domestic	110	(Mean) 42.07	Martins.
Anas	179	(Mean) 42.3	Martins.
Anas		(Maximal) 43.45	Martins.
Anas		(Minimum) 40.8	Martins.
Palmipeds,			Davy, Eydoux,
divers	9	40.6	Brown-Sequard,
longipennes	69	40.6	Souleyet.
Pheasant	5	42.5	Richet.
Hen	17	42.5	Mantegazza, Demarquay, Dumeril, Davy, Prevost and Dumas.
Pigeon	600	(Mean) 41.9	Chossat.
		(Noon) 42.22	
		(Midnight) 41.48	
Pigeon	10	(Mean) 41.2	Corin, Van Beneden.
		(Maximum) 43.6	
		(Minimum) 39.	Daily variation 2.2
Pigeon	31	(Mean) 41.8	Zander.
		(Maximum) 44.	
General mean,		42.0	

Richet[13] considers it probable that the temperature of birds is always above 40° and never, except under extreme conditions, above 44° C.

Further measurements are given by Sutherland Simpson.[14]

2. *Mammals*[15]

Genus or Species.	Temperature.
Pigs	39.7° C.
Sheep	39.6
Oxen	39.5
Rabbits	39.5
Dogs	39.2
Guinea-pigs	39.2
Monkeys	38.3
Horses	37.7
Monotremes	30.0

13 Richet, *loc. cit.*, p. 87.

14 *Proceedings of the Royal Society of Edinburgh*, 1911–12, XXXII, pp. 19–35.

15 Richet, *loc. cit.*, t. III, p. 91.

The monotremes occupy a peculiar position in the scale (Table III). Their internal temperature, while relatively constant and considerably above that of the external air, is notably lower than that of mammals generally.[16] This group probably presents a transition stage between the poikilothermal animals and the homoiothermal animals with a higher body temperature.

TABLE III

Showing Body Temperature of the Monotremes

	Temperature		
	Cloacal	Peritoneal	External
Echidna aculeata, var. typ.	26.5° C.	29.0° C.	21.5° C.
Echidna aculeata, var. typ.	29.5	31.5	22.0
Echidna aculeata, var. typ.	30.5	31.5	18.0
Echidna aculeata, var. typ.	31.5	31.5	18.0
Echidna aculeata, var. typ. young	31.0	31.5	24.0
Echidna aculeata, var. typ. young	34.2	31.5	22.5
Echidna aculeata, var. typ.	34.0	36.0	31.5
Echidna aculeata, var. typ.	28.3	30.0	31.5
Echidna aculeata, var. typ.	28.3	26.9	20.0
Ornithorhynchus paradoxus	24.4	26.9	20.0
Ornithorhynchus paradoxus	25.2	25.2	23.0

The normal diurnal variation in temperature of the human has been studied by many observers. The temperature varies not only with the time of day, but with the taking of food, with age, with external temperature and with other conditions to which we will return later. On the average, the highest temperature is attained in the evening between five and eight o'clock, and the lowest in the early morning between two and six, with upper and lower limits of 37.5° C. (99.5° F.) and 36.3° C. (97.4° F.), respectively. The body temperature may, of course, be greater or less without any necessary implication of disease processes, but the figures given may be considered as fairly representative.[17] It seems well established that, in conditions of health, the daily variation in temperature is about one per cent. of the mean—98.4° F.—expressed in the Fahrenheit scale. It is a peculiar fact also that the

[16] Richet, p. 90, Table II, and C. J. Martin, *Philosophical Transactions of the Royal Society*, London, 1903, Series B, Vol. CXCV, p. 1.

[17] Stewart, "Manual of Physiology," 6th ed., New York, 1910, p. 605.

normal body temperature is fairly close to the upper limits of body temperature compatible with life. A variation of five per cent. from the mean, expressed in degrees Fahrenheit, is often cause for grave anxiety, and a variation of ten per cent. is usually fatal. Compared with this, the variation in body temperature of fishes which live in the water only a few degrees above the freezing point in the winter and in the tepid water of a shallow stream in the summer is enormous.

The highest temperatures recorded in the human, after which recovery has occurred, are shown in Table IV.

TABLE IV

Temperature	Disease Suffered	Observer
43° C.	Hystero-epilepsy	Miersejewski, cited by Lombroso.
42	Typhoid fever	Alvarenga.
42.3	Scarlatina	Bouveret.
43.6	Scarlatina	Vicente et Bloch.
42.2	Periostitis and pyemia	Weber.
43.3	Intermittent fever	Mader, cited by Seguin.
44	Intermittent fever	Hirtz.
44	Intermittent fever	Alvarenga.
44.6	Intermittent fever	Riess.
46	Intermittent fever	Bassanovitz.
46	Intermittent fever	Diez Obelar.
46	Intermittent fever	Capparelli, cited by Richet.
44.8	Intermittent fever	Whitney.
43.3	Rheumatism	Wilson Fox, cited by Seguin.
44.9	Hysterical icterus	Lorentzen.
44	Hysteria	Clemow, cited by Gilles de la Tourette.
45	Hysteria	Lombroso.
45	Hysteria	R. Visioli.
43.6	Hysteria	Sciamanna.
43.9	Fracture of the cervical vertebra	Brodie. Lorain.
44	Fracture of the 12th dorsal vertebra and delirium tremens	Simon.
43.8	Fracture of the 6th cervical (19 hours after traumatism)	Frerichs.

The somewhat alarming but relatively innocuous manifestations of hysteria are attended by a high temperature without the complicating factor of an infection, and pres-

ent, therefore, the effects of temperature alone. It will be noted that the body temperature attained in hysteria—45° C. or 113° F.—and 46° C. in a case of intermittent fever with recovery is nearly as high as we have found recorded—45.7° C. or 114.3° F. after death in a case of tetanus, and is next to the highest recorded, as far as our observation goes, with recovery of the patient. The temperature of the body may, however, rise still higher under the influence of external agents. Thus, in death from strong electric currents, Klein[18] reports a body temperature of 132° Fahrenheit (55.5° C.) or even 140° F. (60° C.) immediately after death.

The effect of temperature upon the contractile manifestations of protoplasm has been summarized by Schäfer:[19]

> In warm-blooded animals the phenomena cease altogether to be exhibited if the protoplasm which is under observation is cooled to below a temperature of about 10° C., although they will be resumed on warming the preparation again, and this even if it has been cooled to 0° C., or a little lower. And when warmed gradually, it is found that the movements become more active as the temperature rises, attaining a maximum of activity a few degrees above the natural temperature of the body, although if maintained at an abnormally high temperature they are not long continued. A temperature a little above this maximum rapidly kills protoplasm, at least that of vertebrates, producing a stiffness or coagulation in it (heat-rigor), which is preceded by a general contraction; from this condition of rigor the protoplasm can not be recovered. But the protoplasm of some organisms will stand temperatures approaching that of boiling water without passing into heat-rigor. Freezing may cause destruction of protoplasm in higher animals, but that of certain of the lower animal and plant organisms is capable of resisting extreme cold, apparently for an indefinite time. This has also been found true for seeds of plants (Dewar).

Frog's muscle (gastrocnemius) reaches its maximum efficiency at about 35° C., after which a falling off occurs as the temperature is increased. Heat-rigor makes its appearance at about 41° C.—about two degrees Centigrade above the usual body temperature of a dog (an

[18] Klein, *New York Medical Journal*, May 30, 1914.

[19] Schäfer, "Text-Book of Microscopic Anatomy," London and New York, 1912, pp. 68–69.

average of 39.38° C. for 176 measurements), or slightly less than the usual body temperature of birds (42° C.).[20]

The maintenance of a constant temperature is dependent not upon one mechanism alone, but upon the coordinated interaction of several mechanisms. The presence of a coat of fur or feathers has long been recognized as a factor in maintaining the constant temperatures of mammals and birds. The development of such a protective covering has many times been emphasized by evolutionists, and seems to be well accounted for on the theory of natural selection. The fur or feathers tend to diminish heat loss from the surface of the body, but have nothing to do with the production or distribution of heat within the body. A subcutaneous layer of fat may still further reduce the heat loss from the surface, as in the Cetacea.

The production of heat is directly dependent upon oxidation in the muscles and glands of the body. A fall of general body temperature is attended by increased muscular activity, as shivering, when the temperature tends to fall unduly low. The muscular activity is dependent in its turn upon the nervous system, and upon the supply of oxygen and oxidizable substances through the blood.

The effect of the blood in maintaining a more nearly constant temperature of the muscles, as well as the production of heat by the muscles themselves, is shown by Meade Smith's experiments on mammalian muscles.[21] Although more heat is produced in a muscle which is contracting than in a resting muscle, there is still some heat production while at rest. When the artery going to a resting muscle was tied off, the difference in temperature between muscle and blood due to heat production in the muscle might be as much as 0.6° C. at the end of a five-minute period. When the circulation is intact, this difference in temperatures does not become so great. Tetanic stimulation of a muscle may lead to a considerable increase in the temperature of the venous blood coming

[20] Richet, "Dictionnaire de Physiologie," 1898, t. III, p. 86.

[21] Meade Smith, *Archiv für (Anatomie und) Physiologie* (Du Bois Reymond), Physiol. Abt., 1881, pp. 105–152.

directly from the muscle as compared with arterial blood.

The distribution of heat is accomplished by the circulating fluids of the body, and particularly by the blood. When the heat loss by radiation from the surface of the body becomes too rapid, the contraction of the walls of the peripheral blood vessels cuts down the quantity of blood going to the surface and, hence, the loss of heat as well. The constriction of the peripheral blood vessels and the contraction of the muscles tend to restrict the lower limit to which the body temperature may fall. The lower the external temperature, the greater the supply of heat from internal combustion needed to maintain the usual temperature of the body unless the radiation be checked by clothing or by artificial heat. It is generally stated that the temperature of the unclothed human body at rest may be maintained until the external temperature falls to 27° C. (Senator). This statement, as will be shown in a later paper, may be open to question. When the external temperature falls below this point, shivering or other involuntary muscular movement begins. This relation between temperature and metabolism accounts in large measure for the large amounts of food sometimes consumed by Eskimos. A young vigorous Eskimo may eat as much as four kilograms (nine pounds) of meat in a day.[22]

K. E. Ranke gives another illustration of the effect of climate upon diet in Germany and in Brazil. Allowing himself a free choice of food, the controlling influence being his appetite, his food requirements were 3,300 to 3,500 calories a day, when the external temperature range was from 15° C. to 22° C. In a dry atmosphere at 25° C., the fuel value of the diet fell to 2,800 calories. In an atmosphere with a temperature of 25° C. to 28° C. and a humidity of eighty-three per cent., the heat value of the diet fell to 1,970 calories in a day. This diet was insufficient

[22] Rink, cited by Lusk, "Fundamental Basis of Nutrition," New Haven, 1914, p. 28.

to maintain his body weight, and disturbances of his general health appeared.[23]

The cold-blooded and warm-blooded animals react differently to changes in external temperature. Thus, the carbon dioxide output of a frog rose from 0.015 gram per kilogram of body weight per hour when the external temperature was 1.6° C. to 0.639 gram when the external temperature was increased to 34° C. (H. Schultz). But as was first shown by Pflüger and his pupils, the metabolism of a warm-blooded animal increases as the external temperature is lowered. If, however, the body temperature is raised there is likewise an increase in the metabolism of the warm-blooded animals. Pflüger regarded the increase in metabolism of the warm-blooded animals accompanying the decrease of external temperature as a later acquisition or as a mechanism which has gradually been evolved in the special interest of a constant temperature. Rubner's measurements of the metabolism in a dog showed an increase from 30.8 calories an hour when the external temperature was 27.4° C. to 40.6 calories an hour when the external temperature was lowered to 11.8° C.,—an increase of about thirty-three per cent. These considerations are sufficient to suggest that the effect of similar changes in the environment may not only not have effects of equal magnitude upon organisms at different levels in the taxonomic scale, but may even have opposite effects at the two extremes of the scale.

The upward march of the body temperature is restricted by the greater access of blood to the periphery and the increased loss of heat by radiation from the surface. A still greater loss of heat, in addition to the rather constant amount lost by evaporation of water from the lungs, is brought about by evaporation of water from the skin or other surface of the body, such as the tongue in dogs. The amount of water on the skin is regulated by the activity of the sweat glands, and these, in their turn, are under nervous control.

[23] Tigerstedt, "Text-Book of Physiology," translated by Murlin, New York, 1906, p. 407.

Animals unable to maintain this constant body temperature throughout the year may maintain a constant temperature during the warmer seasons of the year and hibernate during the winter. This is particularly the case with small mammals, whose relatively large ratio of surface to mass may greatly facilitate heat loss, and with animals whose supply of food is difficult or impossible to obtain during the colder season. The body temperature of the animal falls greatly during hibernation. The importance of size in its relation to metabolism may be shown from the specific energy requirements of various animals. In general, the heat requirement of all well-nourished warm-blooded animals is about 35 calories per hour for each square meter of body surface. But since the surface varies as the square of the dimensions of the body, and the mass varies as the cube of these dimensions, the ratio of surface to mass is much greater in small animals than in large. A mouse requires 452 calories per kilogram of body weight in twenty-four hours, while a horse requires but 14.5 calories and a man about 24 calories in the same time.[24] To sustain a number of mice equal in weight to a man would require more than eighteen times as much food, measured in calories, as a man would need; and more than thirty horses could subsist upon the same amount of food that would be necessary to sustain a number of mice whose aggregate weight was equal to that of one horse. This is very different from saying how much food one mouse as large as a man or a horse would need, and should not, under any conditions, be confused with such a statement.

Milne-Edwards observed that in a small bird such as the sparrow, the body temperature might be lower in winter—40.8° C.—than in summer,—43.77° C.—the difference in temperature amounting to about 3° C.

The heat regulating mechanism of the body is, then, not a simple one but a complex one, involving muscle and gland, food supply and distribution of the blood, the nerv-

[24] Lusk, *loc. cit.*, p. 10.

ous system and the oxygen tension in the blood. We may next consider some of these subsidiary mechanisms.

2. *The Cardiac and Vascular Mechanisms*

The mechanism for the distribution of the blood is in itself a complex one, and involves (1) the mechanism controlling the rate and force of the heart beat and (2) the mechanism controlling the caliber of the blood vessels. When the cardio-regulatory and vasomotor nervous mechanisms are intact, a fall in blood pressure is attended by an increase in the rate of the heart beat; and, conversely, when the blood pressure tends to rise, the rate of the heart decreases. When the extrinsic nerves to the heart are cut, these changes in the pulse rate no longer occur as an accompaniment to the changes in blood pressure. The importance to the animal of these changes in heart rate with changes in blood pressure is shown by the fact that rabbits and dogs whose extrinsic cardiac nerves have been cut soon get out of breath on attempting to run.[25] Through the combined agencies of the vasomotor and the cardio-regulatory nervous mechanisms, the blood pressure in all mammals so far investigated[26] and in some birds, *e. g.*, ducks and fowls,[27] is very much the same, that is, about equal to a pressure of one hundred and twenty-five millimeters of mercury. Changes in the caliber of the blood vessels or in the rate of the heart beat equalize the local changes of pressure due to changes in muscular activity. Working glands or muscles receive, as a rule, more blood than similar organs at rest. This increase in blood-supply may be due in part to the action of metabolites upon the walls of the blood vessels of the active structure (Barcroft).

The blood pressure in the homoiothermal animals, or the blood pressure during the periods of activity of such

[25] See Guthrie and Pike, *American Journal of Physiology*, 1907, XVIII, pp. 27–28, for the earlier literature.

[26] Porter and Richardson, *American Journal of Physiology*, 1908, XXIII, p. 131.

[27] Riddle and Matthews, *American Journal of Physiology*, 1907, XIX, p. 108.

of them as hibernate, is significantly higher than in the poikilothermal animals. The precise significance of this higher pressure in the homoiothermal animals is unknown. It has been suggested that a certain pressure is necessary to overcome the friction of the blood against the walls of the blood vessels. It would appear that fully as much friction might be encountered in the vessels of a turtle weighing thirty or more kilograms as in the vessels of a guinea-pig weighing less than one kilogram. Yet the guinea-pig has the higher blood pressure. Nor does the difference in blood pressure appear wholly due to mere differences in viscosity of the blood of the two forms.

The general stages, from the point of view of function, in the phylogenetic development of the vascular system have been indicated elsewhere.[28]

In connection with the question of the rôle of a more or less constant blood pressure in the animal economy, we may mention the experiments of Legallois, Schiff and Goltz.[29] These investigators found that, while the cells of an animal do not die immediately after the blood pressure reaches a low level, the life of the cells in such an animal as the frog is not possible for indefinite periods of time, and in rabbits or dogs, death is a matter of hours. We may, perhaps, imagine that the low blood pressure may give rise to changes in the chemical systems in the cell that are incompatible with indefinite existence.

3. *The Respiratory Mechanism*

The respiratory movements in mammals, and probably also in birds, are, as Haldane and Lorraine Smith have shown, kept up at such a rate as will maintain a constant tension of carbon dioxide and oxygen in the alveoli of the lungs, and presumably in the blood leaving the lungs. The oxygen and carbon dioxide content of arterial blood may be supposed to be fairly constant in any one indi-

[28] Pike, *Quarterly Journal of Experimental Physiology*, 1913, VII, p. 23.

[29] The literature on the effects of low blood pressure has been given in the *American Journal of Physiology*, 1912, XXX, pp. 444–446.

vidual. The reaction of the body fluids is likewise dependent, in some degree at least, upon the tension of oxygen and carbon dioxide in the blood.

The reaction of the body fluids, particularly the blood, remains remarkably constant during the life of the animal. This is not so much the peculiarity of the higher organisms as is the constant temperature. The process of regulation of neutrality, as Henderson has shown, is a physico-chemical process and depends upon the properties of carbon dioxide, bicarbonates and phosphates in solution. The changes in concentration of hydrogen and hydroxyl ions in the blood are, in their turn, related to the respiratory rhythm.

The whole subject has been so well summarized by Haldane[30] that I venture to quote his statement entire.

To illustrate this point I may perhaps refer to a subject which we have recently been investigating at Oxford. We have found that the respiratory center is so extremely sensitive to any increase or diminution of the partial pressure of carbon dioxide in the blood that a diminution of 0.2 per cent. of an atmosphere, or 1.5 mm. of mercury will cause apnea, while a corresponding increase will double the breathing. The recent researches of Hasselbach have afforded experimental evidence of what had already seemed very probable—that the stimulus to which the center responds is the difference in hydrogen ion concentration, or acidity, brought about by the very slight deficiency or excess of carbon dioxide. He has also investigated quantitatively the effect on the hydrogen ion concentration of the blood of varying the partial pressure of carbon dioxide. From his results and ours it follows that the hydrogen ion concentration of the blood during rest is extraordinarily constant, and remains so day by day and year by year. As the amount of acid and alkali passing into the blood from the food and other sources is constantly varying, it follows that the regulation of hydrogen ion concentration is mainly brought about by the kidneys. It has been known for long that the urine varies in acidity or alkalinity according to the diet; but Hasselbach has measured the actual variations in hydrogen ion concentration. Putting together his conclusions and ours, it appears that during ordinary resting conditions the variations in hydrogen ion concentration of the urine are about a hundred thousand times as great as those of the arterial blood.

Thus the kidney epithelial cells react so delicately to variations in

[30] Haldane, "Mechanism, Life and Personality," New York, 1914, pp. 49–51.

hydrogen ion concentration of the blood, that the very smallest variation in the direction of acidity or alkalinity excites them to excrete a liquid which is, relatively speaking, intensely acid or alkaline, the net result being that the normal hydrogen ion concentration of the blood remains practically constant.

When we have such figures before us we realize the marvellous fineness of the regulation by the kidneys and respiratory center. Physiologists are still so much under the influence of the old gross mechanical theories of secretion that attempts at exact measurements of the delicacy of regulation by the kidneys have hitherto scarcely been made in the case of regulation in other directions, though we have every reason to believe that similar delicacy exists as regards the regulation of the water, salts, and other blood constituents. It is hard to realize that something which looks under the microscope like nothing more than a somewhat indefinite collection of gelatinous material can react, and continue throughout life to react, true as the finest mechanism of highly tempered steel, to the minutest change in its environment.

TABLE V

SOLUBILITY OF GASES IN WATER; VARIATION WITH THE TEMPERATURE

The table gives the weight in grams of the gas which will be absorbed in 1000 grams of water when the partial pressure of the gas plus the vapor pressure of the liquid at the given temperature equals 760 mm.

Gas	8° C.	10° C.	20° C.	30° C.	40° C.	50° C.
O_2	.0705	.0551	.0443	.0368	.0311	.0263
H_2	.00192	.00174	.00160	.00147	.00138	.00129
N_2	.0293	.0230	.0189	.0161	.0139	.0121
Br_2	431.	248.	148.	94.	62.	40.
Cl_2	——	9.97	7.29	5.72	4.59	3.93
CO_2	3.35	2.32	1.69	1.26	0.97	0.76
H_2S	7.10	5.30	3.98	——	——	——
NH_3	987.	689.	535.	422.	——	——
SO_2	228.	162.	113.	78.	54.	——

Whether such a constant O_2 and CO_2 content of the blood of all poikilothermal animals is to be found under all conditions of existence is unknown, but the coefficients of absorption of oxygen and carbon dioxide at varying temperatures would indicate that the carbon dioxide and oxygen held in solution in the body fluids would be subject to change with a change in temperature.[31] In the higher forms, the iron-bearing respiratory pigment, hemoglobin, absorbs all the oxygen with which it combines

[31] Table V, from Table No. 130, p. 142, Smithsonian Physical Tables.

within wide ranges of barometric pressure. There is some difference in the processes of absorption at high and low barometric pressures (Haldane), but the end result is essentially the same. No more oxygen is taken up by the hemoglobin at pressures of two or three atmospheres than at a pressure of half an atmosphere although the amount of oxygen dissolved in the fluid portion of the blood may be greater at the higher pressures. This difference is insignificant compared with the total oxygen in the blood. In the lower forms, manganese in the Echinoderms, and copper in certain Crustaceæ take the place of the iron in the respiratory pigment. The general conditions under which the oxygen is carried in the blood are, however, essentially the same in the various forms.

4. *The Concentration of Sugar in the Blood*

It has been stated since the time of Claude Bernard that the blood in the portal vein at the height of digestion contains more sugar in unit volume than the blood in the hepatic vein. The liver of the homoiothermal animals converts sugar to glycogen and stores it up in that form. Further extensive storage of glycogen occurs in the muscles.

While, under ordinary circumstances, there is good reason to believe that the concentration of sugar in the blood of a given animal is fairly constant for a given set of conditions, it is known that the amounts of sugar in the blood may vary under other conditions. Excessive amounts of sugar in the blood are eliminated by the kidneys. If the concentration of sugar falls, the transformation of glycogen to sugar makes up the deficiency. The concentration of sugar in the blood is not necessarily the same for any two species of animals under essentially the same conditions. Nor does the concentration of the sugar in the blood remain constant in any one individual, cat, dog, or human, under all conditions.[32]

[32] Cannon, *American Journal of Physiology,* 1914, XXXIII, p. 257; Scott, Ibid., 1914, XXXIV, p. 271; Shaffer, *Journal of Biological Chemistry,* 1914, XIX, p. 297.

It is probable that an organ or organs having a glycogenic function exist in some invertebrates, *e. g.*, the oyster, since glycogen may be obtained from these animals. Whether such a delicate adjustment similar to that obtaining in the higher animals between stored glycogen and circulating carbohydrate exists in these forms is unknown to us.

5. *The Osmotic Pressure of the Body Fluids*

In many species of homoiothermal animals, the osmotic pressure of the blood, as measured by the depression of the freezing point, is very constant, nor can it be easily influenced by changes in the environment. The ingestion of large quantities of water may be followed by the secretion of large quantities of dilute urine or by profuse perspiration. A shortage of water to drink leads to the secretion of small quantities of more concentrated urine. Both qualitatively and quantitatively, the physico-chemical constitution of the blood varies within relatively narrow limits.

6. *The Digestive Tract*

The mechanical and chemical processes of the alimentary tract reduce all the food, or its digestible portions, to water-soluble substances, in which form they are absorbed. The proteins of the food are reduced to the amino acids or polypeptids, the starches and sugars to monosaccharides and the fats to soaps before being absorbed.

The introduction of foreign proteins, *e. g.*, egg albumen, as such directly into the blood of the host is injurious. But the amino acids and polypeptids to which this protein is hydrolyzed by the action of the digestive enzymes are, in general, qualitatively the same as those in the blood of the host. The difference in proteins depends upon the difference in the quantitative relations of the amino acids in the protein molecule as well as upon the qualitative differences. The hydrolysis of all proteins to their

simpler splitting before absorption is a mechanism of protection against the entrance of foreign protein into the blood.

The alimentary tract to a certain extent renders the individual independent of the quantitative or stereochemical constitution of the proteins of its food, the only necessity being the presence of certain amino acids in the food.

But efficient as the alimentary tract is, it does not exclude all foreign or inutilizable substances. Cholohematin for example, from sheeps' bile, characterized by a peculiar spectrum and hence susceptible of easy identification, is absorbed by the dog and at least some of it is excreted in the dogs' bile without change.

The protection due to changes in the mucous membrane of the alimentary tract is well shown in the case of arsenic. It was long supposed that the arsenic-eating peasants of the Austrian Tyrol had become immune to the effects of a considerable concentration of arsenic in the blood, since they were able to take large quantities of it by mouth without suffering the usual effects of an overdose. It was shown by Cloetta[33] that the apparent immunity arose from changes in the intestinal mucosa which prevented the absorption of all but a small percentage of the arsenic taken.

If the lower members of the fatty acid series be fed to a dog the body fat which is stored up is softer and of a lower melting point than usual. Excess fat in the food may be stored up as body fat, but under certain conditions, the animal may use as much fat as is taken in the food, and the animal remains in metabolic equilibrium so far as the fat is concerned.

Although the amount of protein necessary to sustain life in an adult or to provide for growth in a young animal varies with the nature of the protein taken in the food, the animal is able to build up its own body protein from

[33] Cloetta, *Archiv für Experimentelle Pathologie und Pharmakologie*, 1906, LIV, p. 196.

any food which contains the requisite amino acids. The power of synthesis of new amino acids in the body is limited. Glycocoll, for example (amino-acetic acid), may be synthesized in the body. More protein is needed as food if its content in certain of the amino acids is low than if its content of these necessary acids is high.[34] But under all the varying conditions, within wide limits, the animal may maintain itself in nitrogen equilibrium, neither storing up any nitrogen in its flesh nor losing any from its tissues. The excess of any particular amino acid above that necessary for tissue growth or repair is eliminated from the body. Voit's famous 35 kilo dog was able to maintain nitrogen equilibrium when fed on amounts of protein varying from 480 grams of meat a day as a lower limit up to 2,500 grams a day.

The quantities of fluid, fat and protein in the blood, while undergoing some changes with the varying conditions of nutrition, starvation and fasting, remain close to a standard concentration as long as life lasts. Variations of great magnitude are incompatible with the prolonged life of the organism.

7. *Epidermis and Other Protective Mechanisms*

In addition to absorption, the limiting membranes of the body have other and important functions. The entrance of many harmful foreign substances into the organism is prevented by the protecting epidermis, the alveolar mucous membrane, and the intestinal mucosa, already noted.

But, however important the exclusion of harmful substances may be, the protection of the organism through the retention of valuable material is also of importance and must be provided for.

The escape of useful substances is prevented by the skin, the liver, the alimentary tract, the lungs and the kidneys. The splitting products of the hemoglobin arising from the death of the red blood cells are separated by

[34] Lusk, *loc. cit.*

the liver in the form of bile pigments, but the iron is conserved for use in the formation of new hemoglobin. But little iron is eliminated by the liver, although much iron may be stored there. The milk of higher animals contains but little iron, and the young mammal needs much iron for the formation of new blood cells during the rapid growth of early life. Provision is made for this by the storage of iron in the liver of the fetus. As postpartum growth proceeds, the amount of iron in the liver is reduced and the amount occurring in hemoglobin is increased.

8. *The Internal Secretions*

The internal secretions form another group of chemical conditions which vary within narrow limits in a state of health. Many years ago Caspar Friederich Wolff expressed the idea that each organ of the body stood in the relation of an organ of internal secretion to some other organ in the body. The liver liberates sugar which is necessary for the action of the muscles, and it also liberates urea which has a definite relation to the action of the kidneys. The muscles set free carbon dioxide which acts upon a particular group of cells in the nervous system, and nitrogenous waste products, some of which are transformed to urea in the liver. But apart from these more general relationships, a system of ductless glands sets free a variety of chemical substances which bear a rather different relation to the development and activity of many other organs and tissues of the body.[35] The relation of the adrenal gland to the myo-neural junction of sympathetic and smooth muscle fiber[36] is well known. The dependence of the development of the secondary sexual characters upon the internal secretion of the sexual glands is also familiar to biologists. The internal secretions in general have become a part of the internal conditions of the organism and of the chemical environment of the cells of the organism.

[35] Mathews, *Science*, 1897, N. S., V, pp. 683–685.

[36] Elliott, *Journal of Physiology*, 1905, XXXII, p. 401.

9. *The Mechanisms for Elimination of Waste Products*

The elimination of waste products occurs promptly and surely. The liver of higher animals not only separates out the useless portions of the hemoglobin derived from worn-out corpuscles (with retention of the iron-bearing part), in the form of bile pigment, but also transforms the ammonia compounds arising from nitrogenous metabolism to the relatively non-poisonous urea. The known chemical functions of the liver[37] are numerous. The kidneys promptly remove the urea and uric acid from the blood as these and other products of metabolism accumulate following activity of the cells. Certain mineral salts, *e. g.*, iron, are excreted by the intestinal mucosa. Some fat, in addition to that which is not absorbed from the food, is also excreted from the intestine.

The attempt to tabulate the various excretions of the body reveals the fact that, although the qualitative composition of the bile and the urine is relatively constant, the quantitative variations are very wide under different conditions. The quantity of carbon dioxide exhaled during twenty-four hours depends upon the diet and upon the amount of muscular activity during the day. Although somewhat disconcerting at first sight, in view of the constancy of internal conditions, this very inconstancy of the excretions is to be regarded as a consequence of the maintenance of constant internal conditions. For it is only by the conservation of those necessary elements or substances whose supply is limited, and the free elimination of waste products or of other substances in excess that the constancy of internal conditions can be maintained. Intake and outgo of matter and energy are such as to maintain relatively constant physico-chemical conditions within the organism. The greater the energy requirements of the organism, the greater must be the intake to meet these requirements, and the greater the amount of waste products eliminated.

37 Hofmeister, "Chemische Organization der Zelle," ein Vortrag; Braunschweig, 1901.

The list of mechanisms, organs and tissues of the animal body and of specific organic or inorganic substances within the body, whose conditions and concentration remain relatively constant, could be extended. The description of these phenomena bulks large in the extensive literature of physiology of to-day. Sufficient data have been adduced to show that there is a considerable basis of fact for the interpretations which we now wish to present. A summary of the known facts of the internal conditions of the organisms permits of the statement that in the homoiothermal animals, there are, then, several mechanisms of extreme delicacy and great constancy under similar conditions and varying but little under wide changes of external conditions. The tracing out of their development constitutes a large part of the subject matter of comparative physiology. But their interpretation rather than their development is the thing of main interest at present. We will return to the questions of the origin and development of these mechanisms in later papers.

What point of view will give us the best insight into the rôle of these mechanisms in the evolution of the vertebrate phylum? Of what use have they been? Or are they simply mechanisms which have arisen in the course of evolution apparently through correlation with other phases of development but without obvious significance to the organism?

III. The Laws of Chemical Equilibrium

Before attempting the interpretation of these mechanisms, or pointing out their rôle in evolution, we may very briefly review the laws of chemical equilibrium as exemplified in the "slow" reactions of the physical chemist. For our present purpose, these laws may be included under the law of mass action, Van't Hoff's law and the phase rule. A fuller statement is given in Blackman's paper and in the text-books of physical chemistry.

1. *The Law of Mass Action*

The mass law or law of mass action expresses the relationship between the molecular concentration and the speed of the reaction. The concentration of the substance is usually expressed in terms of the number, either whole or partial, of gram molecular weights or gram molecules present in one liter of the solution. On the basis of Avogadro's law, there is the same number of molecules of sodium chloride in a gram molecule (58.4 grams) of sodium chloride as there are molecules of cane sugar in a gram molecule (342 grams) of cane sugar or molecules of oxygen in a gram molecule (32 grams) of oxygen. If equal fractions of the gram molecular weights of two different substances are each dissolved in a liter of water, there will be the same number of molecules in each of the two solutions.

Let two substances, A and B, be present in a solution in the concentrations (expressed in gram molecules) of c_A and c_B, respectively, at any stage of the reaction $A + B \rightarrow C + D$ and let the temperature remain constant throughout the action. The speed (S) of the forward action expressed in gram molecules of A and B transformed in unit time is defined by the relation $c_A \times c_B \times F = S$ where F is the affinity constant. As the reaction proceeds, c_A and c_B and, hence S, steadily decrease, since A and B are being continually used up. S may therefore be taken at any time as the quantity of A and B which would be transformed in the unit of time if the concentration c_A and c_B were maintained at a constant value by the continual addition of new substance. F is the measure of the intrinsic activity (affinity) which is the driving force in the reaction, and is independent of the concentration. If unit concentrations are taken, $c_A = c_B = 1$ and $F = S$. The activity, F, is thus represented numerically by the number of gram molecules transformed in unit of time when each reacting substance is present in unit concentra-

tion. Since c_A, c_B and S may be measured at any time, F may be calculated for any action.[38]

The law of molecular concentration or law of mass action is: In every chemical experiment, the speed of the action at any moment is proportional to the first, or some higher, power of the molecular concentration, at that time, of each interacting substance and to the intrinsic activity (affinity) of the substances.

2. *Van't Hoff's Law*

But the speed of any reaction at any concentration varies with the temperature. In general, the increase in speed is about ten per cent. for each increase of one degree Centigrade, or, as it is sometimes expressed, the speed of the reaction is doubled when the temperature is increased ten degrees Centigrade. This is known as Van't Hoff's law. The actual change in the speed of the reaction may be greater or less than ten per cent. for each change of one degree Centigrade, and is usually expressed by a coefficient. When the coefficient is 1.2 or less, that is, when the change in speed is two per cent. or less for each change of one degree Centigrade, the action is usually considered to be a physical and not a chemical action. When the temperature coefficient is greater than 1.2, the action is commonly considered to be a chemical action. No theoretical explanation of Van't Hoff's law of change in speed with change in temperature has so far been advanced.

These laws apply to reactions which go on at a measurable speed and which have been called "slow" reactions by the physical chemists. These "slow" reactions are to be distinguished from those reactions which proceed so rapidly that no measurement of their speed at different intervals is possible, or reactions of the explosive type.

[38] Smith, "General Inorganic Chemistry," 1st ed., New York, 1906, p. 251.

3. *The Phase Rule*

One other principle of physical chemistry finds frequent application in biology, and that is the phase rule developed by Gibbs. The phase rule defines the condition of equilibrium existing in a system by the relation between the number of coexisting phases and components. "According to it a system made up of n components in $n+2$ phases can only exist when pressure, temperature and composition have definite fixed values; a system of n components in $n+1$ phases can exist so long as only one of the factors varies and a system of n components in n phases can exist while two of the factors vary. In other words, the degree of freedom is expressed by the equation

$$P + F = C + 2, \text{ or } F = C + 2 - P,$$

where P designates the number of phases, C the number of components, and F the degree of freedom."[39] In other words, F represents the number of conditions which may be varied without causing one of the phases to disappear.

An example of the phase rule, based upon the properties of a familiar substance, is that of ice, liquid water and water vapor existing together in a closed vessel from which the air has been exhausted. Ice, liquid water and water vapor each constitute a phase of the system, and there is but one component or substance—water—present. Here, one component exists in three different phases. We have, then, n components and $n+2$ phases. The essential conditions for the existence of the system are temperature and pressure of the water vapor. In the notation quoted above, $P=3$, $C=1$. Hence, $F=1+2-3=0$. Neither of the conditions—temperature or pressure—of the system can be changed without causing one of the phases to disappear. There is no degree of freedom, or, as it is sometimes expressed, the system is a non-variant system. The exact conditions for stability

[39] Morgan, "Physical Chemistry," New York, 1911, p. 119.

of such a system are a pressure of water vapor equal to 4 mm. of mercury and a temperature of .007° C. above 0° C.—the freezing point at atmospheric pressure.

Many applications of the phase rule to living matter have been made. We will cite but one. The globulins—typical proteins found in the blood of animals—are insoluble in distilled water, but are soluble in dilute solutions of the inorganic salts, such as sodium chloride. The globulin may exist in a system of water, sodium chloride and globulin, as globulin in solution or as precipitated globulin. The globulin is the only component existing in more than one phase under the conditions of the experiment.[39a] Addition of water to the system to such a degree that the concentration of the inorganic salts falls below a certain minimum leads to a precipitation of part of the globulin in solution. The removal of the mineral salts, keeping the volume of the solution constant, will also lead to precipitation wholly or in part, of the globulin in solution. But whether water be added or salt removed, the essential condition which undergoes changes is the concentration of the salt. Pressure does not enter in as one of the conditions of the system. And if the temperature of the system be raised above a certain point, depending upon the globulin present in the system, the globulin will be precipitated. In this system, the number of components is one (globulin) and the number of phases is also one, dissolved globulin. We have, therefore, a system of n components with n phases, and two of the conditions may vary, within certain limits, at the same time, viz., the concentration of the sodium chloride and the temperature. In the terminology of the quotation above, $P=1$, $C=1$ and $F=1+2-1$, or 2. This is also expressed by saying that the system is divariant. This system is of interest because of the fact that it also illustrates the phenomena of maximum points.

[39a] While globulin is not the only component entering into the system, we have restricted the discussion to the department of the globulin for reasons of space and simplicity.

Further details should be sought in the text-books of physical chemistry, and especially those by Bancroft and Findlay on the phase rule.[40]

IV. The Interpretation of the Regulatory Mechanisms in Terms of Chemical Equilibrium

But what evidence is there that the laws of mass action or of chemical equilibrium apply to living matter? Is there any evidence that the reactions occurring in the cell are "slow" reactions similar to those of the physico-chemical laboratory? The answer to these questions is decidedly in the affirmative. Much evidence in favor of such a view was presented by Blackman. Hofmeister, Bredig and others regard the cell as a congeries of enzymes, each one, according to Hofmeister,[41] acting in its own compartment upon its own peculiar substrate.

1. *Applications of Van't Hoff's Law*

As further evidence of the nature of the reactions in living matter, we may cite the work of Shelford[42] on tiger beetles, in which the length of the combined quiescent periods of the pupal and the prepupal stages was increased from four or six weeks at a temperature of 28° to 30° C. to ten or twelve weeks at a temperature of 15° to 17° C. Riddle[43] found that the temperature coefficients for digestion in *Amia, Rana, Necturus* and the common turtle (*Emydoidea*) ranged from 0.93 in *Necturus* to 7.81 in the turtle. Rogers and Lewis[44] have recently shown that the temperature coefficient of the rate of contraction of the dorsal blood vessel of the earthworm is of the order of magnitude to be expected if the processes

40 Bancroft, "The Phase Rule," Ithaca, New York; Findlay, "The Phase Rule and Its Applications," 3d ed., 1911, London and New York.

41 Hofmeister, *loc. cit.*

42 Shelford, *Linnean Society's Journal*, 1908, XXX, p. 176.

43 Riddle, *American Journal of Physiology*, 1909, XXIV, pp. 447–458.

44 Rogers and Lewis, *Biological Bulletin*, 1914, XXVII, p. 269. See also Lehenbauer, "Physiological Researches," 1914, I, pp. 247–288.

concerned are of the nature of slow chemical reactions. The application of Van't Hoff's law in these instances is sufficiently plain.

Considering the processes in living matter, from this point of view, we may gain some insight into the reason why so many of the factors or conditions entering into the reactions occurring in the body of a higher organism should be kept as nearly constant as possible.

2. *The General Conditions of the Reactions in the Cells*

In determining the velocity of a reaction, we may determine (1) what quantity of the reacting substances combine or react in unit time, the usual method of the laboratory, as has been shown above, or (2) we may determine what quantities of material must be added in unit time to keep the reaction going at a constant rate. Recalling now the nearly constant factors in the higher mammalian organism, the oxygen content, the temperature, and the hydrogen ion concentration all varying within relatively narrow limits, and the variations usually being in such a direction as to get more material to an active or working structure in unit time, we can see that there are certain very effective devices for maintaining a reaction at a constant speed, which are the counterparts of the apparatus employed in the chemical laboratory. But the mechanisms in the living organism are capable of regulating, with a great degree of exactness, more conditions than any artificial mechanisms so far devised in the laboratory can control.

In the evolution of the organism the development of the various regulating mechanisms which we have described has brought about a set of conditions which tend to keep the environment surrounding the cells relatively constant. The analogy beween the reactions in the cells and the slow reactions of the physical chemist becomes clear. The temperature of the body being constant, the reactions in the cells, dependent as they are, upon a constant supply of material, go on at a relatively constant rate, or at such a rate as is determined by the needs of

the organism, and a rate which is provided for by the changing distribution of the blood.

Not all the physico-chemical conditions of cell activity are as constant as those discussed in the second division of this paper. Nor does the experimental interference with certain body structures leading to known departures from the usual conditions always entail serious results. As an instance of this we may cite the experiments of Ogata,[45] who investigated the rate of absorption of protein when fed by the mouth as compared with its rate of absorption when introduced directly into the intestine through a fistula. Taking the nitrogen output in the urine as the expression of the rate of absorption, the nitrogen output rose much more rapidly after direct introduction of the meat into the intestine than it did when the meat was fed by mouth. Although the absorption of the food was apparently more rapid than usual, the capacity for adjustment on the part of the organism was not exceeded. We may mention in passing that one function of the stomach may be to act as a storehouse and provide for a more gradual absorption of food than would otherwise occur. In the terminology of this paper, there is a less sudden entrance of constituents tending toward a disturbance of the equilibrium when the stomach is present than when it is absent. If food is administered in small portions and in a finely divided state after complete removal of the stomach, life goes on as usual (Czerny). But one is hardly justified in saying that, because great and profound changes do not occur in the organism after extirpation of the stomach, the stomach has no important function.

A detailed consideration of the inconstant or variable conditions and of the manner and extent to which changes in the environment can influence all internal conditions, must be deferred for another communication. Enough has been said in these pages to show, in outline at least, the essential uniformity of some important internal con-

[45] Ogata, *Archiv für Anatomie und Physiologie*, 1883, p. 89.

ditions of the higher organism and to indicate their rôle, on the assumption that the internal mechanisms of the organism are physico-chemical mechanisms.

In the response of the respiratory mechanism to the increased concentration of carbon dioxide or to lack of oxygen in the blood, we have an instance of adaptation which is not at once seen to be an obviously automatic and inevitable result of the physico-chemical properties of the environment. A striking characteristic of the respiratory center is at once its sensitiveness to slight changes in the concentration of carbon dioxide and its tolerance to the accumulation of carbon dioxide in the blood. The respiratory cells react to an extremely slight increase of carbon dioxide which is insufficient to affect the other cells, and remain sensitive to this increase after the concentration has risen so high that the visible responses of certain other cells have ceased. The common excitability of the respiratory and other motor nerve cells to carbon dioxide may be supposed to result from the disturbance or change produced in a complex system by the accumulation of one end product of the reaction, and to this extent to be an automatic result of the physico-chemical constitution of the cell.

The question raised by Mathison[46] as to whether carbon dioxide is a stimulant for all nerve cells is of interest in this connection. Carbon dioxide is certainly a stimulant for the central nerve cells of the respiratory mechanism, but it is not necessarily a stimulant to the same degree for all nerve cells. It is probable that all living matter is more or less sensitive to the accumulation of carbon dioxide since it is one of the waste products of all destructive metabolism. The cell bodies of the respiratory neurones, by reason of the development of this common property of excitability to carbon dioxide, have become especially adapted to respond to slight variations in carbon dioxide. The adaptation undoubtedly depends upon a physico-chemical change in the respiratory neu-

[46] *Journal of Physiology*, 1910, XLI, p. 448.

rones. The persistence of the common property accounts for the asphyxial convulsions of the spinal animals and for the movements which are sometimes considered to be respiratory movements and commonly attributed to so-called respiratory centers. But whether we consider that the cells of the respiratory group have gradually acquired a lower threshold value for stimulation by carbon dioxide than the other cells of the nervous system, or that the cells of the respiratory group have simply retained the the common excitability of protoplasm in general to carbon dioxide, and the remaining cells have undergone modifications which have raised their threshold value, makes little difference from the theoretical point of view. In an environment which is, so far as one can determine, uniform, certain quantitative variations have occurred which have resulted in a differential sensitiveness to carbon dioxide or to lack of oxygen. The changes have not been qualitative, since asphyxial convulsions involving muscles innervated from other parts of the central nervous system, may be brought on by a reduction of the oxygen supply.

The usefulness of the lower threshold value for lack of oxygen in a particular group of cells is at once apparent. Oxygen generation of the blood and elimination of carbon dioxide proceed without attention, and without noticeable excitation of any other group of nerve cells. There is no disturbance of the precision of movement of any group of muscles aside from those actually engaged in the respiratory act, nor the slightest effect upon the neurones involved in mental processes, resulting from the decreased oxygen or increased carbon dioxide tension in the blood sufficient to provoke a respiratory response.

3. *Stimulation in Terms of Chemical Equilibrium*

This brings us to a consideration of the nature of stimulation in general. Lack of space precludes all but the briefest mention at this time. We may here simply indicate the consideration in terms of the laws of mass

action and of the phase rule. That changes in the speed of reaction depend upon the concentration of the reacting substances or of the end products of the reaction has been shown in the discussion of the laws of mass action. It is not difficult to see that the respiratory movements owe their origin largely to changes in concentration of carbon dioxide and oxygen, and, since these changes result in a slight change in the concentration of the hydrogen ions it is not difficult to imagine that the law of mass action may be involved in the stimulation of the respiratory cells in the medulla oblongata. We have given in the third section of this paper two illustrations of conditions coming under the operation of the phase rule. It is true that living matter undoubtedly comprises vastly more complex systems than those described, but that the general principles underlying the reactions are similar in most important respects to the systems employed in laboratory experiments is scarcely to be doubted. The withdrawal of water from a cell or nerve fiber by osmosis or drying, entailing a quantitative change in the amount of water in the cell, is followed by other changes in the cell which tend to bring about a reestablishment of conditions in accordance with the laws of chemical equilibrium. That a change of phase of some of the components occurs in the process is probable.

Such influences as drying, applications of heat or mechanical pressure, whether occurring in the laboratory or in nature, are known as stimuli, and the changes associated with their operation in the organism are responses to stimulation. As Jost[47] has pointed out, the formal conditions of existence may act as stimuli to organisms. Although we must admit that a wide gap still exists, it seems to us that the discussion of stimuli and the processes of stimulation in terms of the law of mass action and the phase rule will enable us to meet in some degree, however small, Haldane's objection[48] that no causal con-

[47] Jost, "Pflanzenphysiologie," zweite Aufl., p. 618, Jena, 1908.

[48] Haldane, *loc. cit.*, p. 37.

nection has been shown between stimulus and response. And we may hope that here as elsewhere in biology the limits to our knowledge of nature will gradually be broken down.

The accumulation of waste products in the blood or body fluids through increase of their concentration in these fluids, leads to modified activity of the excretory and other organs. We cite a few examples.

The kidney, in addition to the elimination of water, follows the law of mass action in other ways. The volume of urinary secretion, other things being equal, is proportional to the volume of blood flow through the kidneys in unit time. The greater volume of blood carries with it a greater volume of waste products in unit time, and hence a greater volume of secretion is the result to be expected if urinary secretion is a physico-chemical process following the general provision of the mass law.

The accumulation of waste products arising from the slow reactions in the cells gives rise to the phenomena of fatigue, and the general slowing down of the cell processes, just as the accumulation of the end products of any slow reversible reaction decreases the amount of chemical transformation in unit time, in accordance with the mass law.

Excess of carbon dioxide, a typical waste product, even of the activity in nerves,[49] decreases or abolishes the conductivity of a nerve fiber. A stimulus (geotropic) may be applied to a plant in an oxygen-free atmosphere, but the responses will not occur until the plant is moved to an atmosphere containing oxygen.[50]

But even waste products in a certain concentration may be necessary for the optimum conditions of activity of an organ. Baglioni[51] points out that the selachian heart maintains its activity better in a solution of the inorganic salts containing two per cent. urea—the normal

[49] Tashiro, *American Journal of Physiology*, 1913, xxxii, p. 107.

[50] Jost, "Pflanzenphysiologie," zweite Aufl., p. 524, Jena, 1908.

[51] Baglioni, *Zeitschrift für allgemeine Physiologie*, 1906, VI, p. 71.

concentration of this substance in selachian blood—than in similar solutions without the urea.

V. General Considerations and Summary

The higher organisms have, therefore, developed a system of regulation by means of which internal conditions are kept relatively constant. This mechanism consists essentially of a physical means of distribution of material and heat—the circulatory organs and fluids—whose composition varies within narrow limits, a muscular, a glandular and a nervous mechanism for regulating the temperature, and a system of excretory organs for removing the waste products from the circulating fluids. Both chemical and nervous mechanisms of coordination are involved. The variations in the composition of the circulating fluids are such as will provide greater quantities of easily utilizable material at a time when it is needed. The internal secretions are important agents in maintaining the organism at a high pitch of efficiency through their influence upon the neuro-muscular apparatus and the general metabolism of all the tissues and organs. Regardless of the variations in external conditions, so long as these do not transcend the limits within which life is possible, and barring physical accidents or disease, the internal mechanisms keep it always fit, whether for work or rest, for battle or for play.

We have heard much about the survival of the fittest, and about the rôle of the strong jaw and powerful teeth and other physical characteristics in the struggle for existence. The doctrine of evolution, so far as its morphological side is concerned, may be regarded as fairly well founded. A little reflection, however, will show that the morphological aspect is only one phase of the problem. What profits it an animal to possess strong muscles and sharp teeth unless these muscles shall be at all times ready to contract quickly and surely? What if it become engaged in combat with an adversary and its muscles be

sluggish from cold? Or, supposing the temperature to be favorable, it be not able to control those muscles accurately and sink its teeth into the vital spot of the enemy? The answer is simple; another skeleton will soon lie bleaching. Somewhere or other evolution must have been concerned with the functional side. One protective mechanism has been suggested by the slow action of muscles in the cold and their more rapid action at higher temperature. The combat between a dog and a snake may be a fairly even one when the weather is warm, and very much in favor of the dog when the weather is cold. There is a strong presumption that the elaborate and complicated nervous vascular and glandular mechanisms, some or all of which are developed in birds and mammals, have some bearing on the general problem of evolution. It has rendered them far more independent of the environment than poikilothermal animals are. There is not so much necessity of hibernation during the winter, and a frosty morning is as good as any for hunting.

And if we consider that the changes of energy and material underlie all the other changes in the organism, regardless of the source from which they arise, it will be apparent that at least one part of the final discussion of evolution will be in terms of the changes of matter and energy within the organism.

The problems of the general processes of evolution—the adjustment of the animal to its environment or responses to changes in it, variation, adaptation, heredity and geographical distribution, and even the biochronic equation (De Vries) may all be approached from the point of view of the experimental physiologist. The consideration of these subjects will be taken up in subsequent papers.